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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/139,425 | 08/25/1998 | CHARLES T. ESMON | OMRF-171 | 5290 |

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| EXAMINER | |
|---|---|
| KAUSHAL, SUMESH | |
| ART UNIT | PAPER NUMBER |
| 1636 | 26 |

DATE MAILED: 09/11/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/139,425 | ESMON ET AL. | |
| | Examiner | Art Unit | |
| | S. Kaushal | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,13-16,19-23 and 25* is/are rejected.

7)☒ Claim(s) *2-11,16-18 and 24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## *DETAILED ACTION*

The finality of the rejection of the last Office action is withdrawn in view of new grounds of rejections below:

Applicant's response filed on 06/11/02 has been acknowledged.

*Claims 1-25 are pending and were examined in this office action.*

► *If the claims are amended, added and/or canceled in response to this office action the applicants are required to follow Amendment Practice under 37 CFR § 1.121 (http://www.uspto.gov) and A CLEAN COPY OF ALL PENDING CLAIMS IS REQUESTED.*

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for selectively delivering molecule to the nucleus of endothelial cells of the large vessels by administering a conjugate of an agent that bind selectively to the endothelial protein C receptor (EPCR), does not reasonably provide enablement for the treatment of any and all diseases or disorders in an individual. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention **commensurate in scope** with these claims.

The scope of instant claims encompasses a method for selectively delivering any and all molecules (proteins, DNA, antisense or synthetic compounds) to the nucleus of endothelial cells of a the large vessels by administering a conjugate of an agent that bind selectively to the endothelial protein c receptor (EPCR) and treat of any and all diseases or disorder in an individual.

At best the instant specification disclose the selectively delivering molecules of interest to the nucleus of endothelial cells of the large vessels by administering a conjugate of an agent that bind selectively to the EPCR. The specification discloses the selective delivery of streptavidin by using biotin labeled EPCR monoclonal antibodies (spec. page 13-14, example 3-4). In addition the specification teaches the transport of radio-labeled Activated Protein C (APC) to the nucleus of endothelial cells expressing EPCR (spec. page 14, example-5). However the instant specification fails to disclose the treatment of any and all disease or disorder using any and all therapeutic molecules conjugated to an agent that bind selectively to EPCR.

The word "treatment" means administration or application of remedies to a patient or for a disease or an injury; medicinal or surgical management; therapy. The substance or remedy so applied[1]. Furthermore, considering the scope of therapeutic molecules (as claimed), it is unclear whether the disease would be the result of the loss of a gene product or is the result of altered gene product function. It is even unclear whether the treatment of the disease in the context would require increase or decrease in the expression of the gene product. Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed. The earlier office action clearly states that Gene therapy is considered

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[1] *The American Heritage® Dictionary of the English Language, Third Edition* copyright © 1992 by Houghton Mifflin Company..

highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations (Anderson WF, Nature 392:25-30, 1998; Verma et al Nature 389:239-242, 1997 *ref. of record*). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectations of current gene therapy protocols have been over sold without any apparent success. The advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease. (see Orkin).

Furthermore, the scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). The courts have clearly stated that: "A specification did not disclose what is well known in the art. See, e.g., Hybritech Inc. V. Monoclonal Antibodies, Inc., 802 F. 2d 1367, 1385, 231 USPQ 81, 94(Fed. Cir. 1986). However, that general off-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific material or of any of the conditions under which a process can be carried out, undue experimentation is required: there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. *It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".* Genentech Inc. V. Novo Nordisk A/s, 42 USPQ2d 1005 (CAFC 1997).

In instant case the use of any and all molecules (as claimed) to treat any and all diseases or disorders by delivering the molecule to the nucleus via EPC-receptor is not considered routine in the art, and without sufficient guidance to a specific therapeutic molecule the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 13, 15, 20 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Foster et al (US 5225537, 1993).

Foster teaches construction of a PAP-C fusion protein by using site directed mutagenesis to fuse PAP-I coding sequence with Protein C DNA. PAP-I is an anticoagulant protein (Col.17, example 3-4). The cited art further teaches a hybrid activated protein C comprising at least one lipocortin phospholipid-binding domain joined to a gla-domainless activated protein C (col22

line 11-23). The cited art teaches the coupling of protein C and activated protein C to PAP and lipocortin domains at molecular level. Therefore the cited art clearly anticipates the fusion protein coupling means as claimed.

Claims 13, 15, 20 and 22-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Eibl et al (US 5571786, 1996).

Eibl teaches a conjugate wherein the Activated Protein C is attached to thrombin coupled to CNBr-Sepharose 4B (col.6, example-3). The cited art teaches the attachment of a protein (thrombin) to activated protein C. The cited art further teaches the attachment of thrombin-activated protein C complex to a polymer (CNBr-Sepharose4B). Thus the cited art clearly anticipate the conjugate as claimed.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 is indefinite because it is unclear what is "fragments thereof binding to EPCR" in this context.

Claim 14 is indefinite because it is unclear what is "recombinant molecule based thereon" in this context.

***Conclusion***

No claims are allowed.

Claims 2-12, 14, 16-19, 21 and 24-25 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten independent form including all of the limitation of the base claim and any intervening claims.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

- Foster et al, US 5766921, 1998.
- Fukudome et al US 6399064, 2002.
- Fukudome et al US 5695993, 1997.
- Esmon et al US 5202253, 1993.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 9:00 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Irem Yucel Ph.D. can be reached on (703) 305-1998. The fax-phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Zeta Adams, whose telephone number is (703) 305-3291.

*S. Kaushal*
**Patent examiner**

TERRY MCKELVEY
PRIMARY EXAMINER